## III. REMARKS

**Preliminary Remarks**

Reconsideration and allowance of the present application based on the following remarks are respectfully requested. Claims 1-22 are currently pending in this application. Claims 1-15 and 18-22 have been withdrawn from consideration for allegedly being drawn to a non-elected invention. Claims 16 and 17 remain at issue. This response is timely filed as it is accompanied by a petition for an extension of time to file in the third month and the requisite fee.

On page 2 of the official action, the examiner objected to the priority of this application for allegedly lacking the specific reference to the earlier filed application. The applicants have amended the specification to specifically refer to the proper priority (see also inventor declaration/power of attorney and original application transmittal forms for original priority claim).

On page 3 of the official action, the examiner objected to claims 16 and 17 for being dependent upon a non-elected claim. Amended claim 16 is directed to a method of enhancing apoptosis of a target cell by administering a therapeutically effective amount of an immunoconjugate to a subject, wherein said immunoconjugate comprises an anti-CD20 antibody or an immunogenic fragment thereof that binds to CD20 expressed by a target cell that is to be eradicated, wherein said anti-CD20 antibody or immunogenic fragment thereof possesses human effector function, and further wherein said anti-CD20 antibody or immunogenic fragment thereof is fused as its carboxy terminus to IFN-α-2a that binds a receptor expressed on the surface of an effector cell. Amended claim 17 is directed to the method of claim 16 wherein the target cell is a B cell lymphoma cell. Support for amended claims 16 and 17 can be found throughout the specification, for example, originally filed claim 1 and Example 1. In view of the foregoing amendment, the applicants submit that claim 16 is now in independent form, claim 17 depends from independent claim 16, and new claims 23-26 depend from claim 16 as well.

New claim 23 is directed to a method of claim 16 wherein the effector cell is a cell which expresses an IFN-α-2a receptor selected from the group consisting of natural killer (NK) cells, lymphocyte-activated killer (LAK) cells, macrophages, monocytes, and polymorphonuclear (PMN) cells. Support for new claim 23 can be found throughout the specification, for example, in paragraph 29.

New claim 24 is directed to the method of claim 16, wherein said immunoconjugate facilitates extracellular (ADCC-type) and/or intracellular (phagocytic) killing of target cells. Support for new claim 24 can be found throughout the specification, for example, originally filed claim 1.

New claim 25 is directed to the method of claim 16, wherein said immunoconjugate comprises an anti-CD20 antibody or an immunogenic fragment thereof selected from the group consisting of Rituximab, 1F5, Ibritumomab, 1H4, and anti-B1 antibody. New claim 26 is directed to the method of claim 16, wherein the immunogenic fragment is selected from the group consisting of a single variable region of the anti-CD20 antibody VL or VH, two or more variable regions, domain deleted antibody and minibodies, Fab, Fab1, Fab2, SFV, and single chain antibodies. New claim 27 is directed to the method of claim 16, wherein the anti-CD20 antibody or immunogenic fragment is a humanized or chimeric antibody. Support for new claims 25-27 can be found throughout the specification, for example, in paragraphs 6, 31, 35 and 36. The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

**Patentability Remarks**

***Rejection Pursuant to 35 U.S.C. §103(a)***

On page 4 of the official action, the examiner rejected claims 16 and 17 under 35 U.S.C. §103(a) as allegedly being obvious over Demidem *et al.*, *Cancer Biother. Radiopharm.*, 12:177-186 (1997; hereafter "Demidem") in view of Hagenbeek *et al.*, *J. Clin. Oncol.* 16:41-47 (1998; hereafter "Hagenbeek") and Reff *et al.*, *Blood* 83:435-445 (1994; hereafter "Reff"). The examiner also rejected claims 16 and 17 under 35 U.S.C. §103(a) as allegedly being obvious over Davis *et al.*, *Clinical Cancer Research* 6:2644-2652 (2000; hereafter "Davis") in view of Taji *et al.*, *Jpn. J. Cancer Res.* 89:748-756 (1998; hereafter "Taji"). In view of the foregoing amendment and remarks, the applicants respectfully traverse.

*Demidem in view of Hagenbeek and Reff*

With regard to Demidem in view of Hagenbeek and Reff, the examiner alleged that Demidem teaches that an anti-CD20 antibody enhances apoptosis of B cell lymphoma cells when used as a pretreatment before administration of cytotoxic drugs. The examiner further asserted that Hagenbeek teaches how to make and purify the human recombinant interferon-α-2a (hereafter "IFN- α-2a") and use it to treat patients with B cell lymphoma (stages 3 and 4 of malignant non-Hodgkin's lymphoma). The examiner also alleged that Reff teaches how to make a fusion protein of anti-CD20 antibody or a fragment thereof to IFN- α-2a. The examiner further alleged that it would have been obvious to one of skill to fuse the carboxy terminal of an anti-CD20 antibody or fragment thereof to IFN- α-2a and expect success in enhancing apoptosis of B cell lymphoma cells. The examiner concluded that one of skill would have been motivated to make such a fusion to minimize painful injections by giving one fusion protein instead of two separate injections.

A *prima facie* case of obviousness requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicants' invention in the combined prior art references; and (3) a reasonable expectation of success. M.P.E.P. § 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Moreover, the prior art must provide some teaching, suggestion or motivation to make the **specific** combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis added) (citing *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

The applicants submit that the primary reference, Demidem, fails to teach or suggest a method of enhancing apoptosis of a target cell by administering a therapeutically effective amount of an immunoconjugate to a subject, wherein said immunoconjugate comprises an anti-CD20 antibody or an immunogenic fragment thereof that binds to CD20 expressed by a target cell that is to be eradicated, wherein said anti-CD20 antibody or immunogenic fragment thereof possesses human effector function, and further wherein said anti-CD20 antibody or immunogenic fragment thereof is fused as its carboxy terminus to IFN-α-2a that binds a receptor expressed on the surface of an effector cell. Specifically, Demiden only

teaches that the murine chimeric antibody C2B8 sensitized DHL-4 B cell lymphoma cells via a possible modulation of the anti-apoptotic response, or an inhibition of protective proteins to allow such agents as ADR (interfere with DNA replication), CDDP (interfere with DNA replication), TNF-α (mediate programmed cell death), DTX (mediate programmed cell death and inhibits protein synthesis), and ricin (inhibits protein synthesis) to be effective against the B cell lymphoma cells. **This inhibition was not predictable**. For example, Demiden also teaches that C2B8 did not sensitize DHL-B lymphoma cells to VP-16, a topoisomerase II inhibitor. Thus, Demiden teaches that C2B8 antibody inhibits some protective measures used by DHL-B lymphoma cells. When this inhibition occurred, the C2B8 antibody lowered these cells' ability to resist **subsequent treatment** with certain cytotoxic agents. The applicant submits that nowhere in the teachings of Demiden is there a discussion or suggestion of using an anti-CD20/ IFN-α-2a fusion protein as a **single vehicle for targeting cell mediated cytotoxicity of B-cell lymphoma cells via the subject's own natural killer cells and/or macrophages** (for example).

The applicant's claimed method uses a fusion protein comprising anti-CD20 antibody or immunogenic fragment and IFN-α-2a. This unique fusion protein allows for **specific targeting of tumor cells to attract and potentiate** cell-mediated cytotoxicity either by antibody-dependent cell-mediated cytotoxicity, phagocytic or direct killing. This cell mediated cytotoxicity only occurs because the subjects own natural killer cells, polymorphonuclear cells, lymphocyte-activated killer cells, macrophages, and monocytes recognize the IFN-α-2a portion of the novel fusion protein. In stark contrast, Demiden only teaches using medicinal cytotoxic agents to kill B-cell lymphoma cells that have had their resistance pathways altered by pre-treatment with a mouse anti-CD20 antibody.

In addition to these shortcomings, Demiden requires a two step method. The first step is sensitizing DHL-B lymphoma cells with C2B8 antibody. The second step is then treating the sensitized DHL-B lymphoma cells with a cytotoxic agent. The applicant has disclosed a method for enhancing apoptosis of tumor cells that comprises only one step. This method step is the administration of the applicant's immunoconjugate comprising an anti-CD20 antibody fused to IFN-α-2a to a subject whose own cell mediated cytotoxic acting cells (*i.e.*, natural killer cells, macrophages *etc.*) kill the B cell lymphoma cells. Therefore, one of skill in the art, studying the disclosure of Demiden in view of the contradictions, would not be taught or even suggested to practice the claimed invention.

With regard to the secondary reference, Hagenbeek, the applicant respectfully submits that this reference does little to overcome the failings of the primary document (Demiden)

and, in fact, teaches away from the claimed invention. Specifically, Hagenbeek does not teach a method wherein an immunoconjugate fusion protein pinpoints B-cell lymphoma cells and enhances apoptosis via interferon. Rather, Hagenbeek simply teaches interferon can be used as a maintenance treatment measure to prolong the time of re-progression of B cell lymphoma cells after chemotherapy. Hagenbeek does not teach or suggest targeting tumor target cells expressing CD20 and in fact, concludes its study by stating the overall survival rate was not influenced by interferon treatments. Accordingly, the applicants respectfully submit that one of skill in the art would not have been motivated to use inteferon as a means to cause apoptosis in B-cell lymphoma cells by fusing IFN-α-2a to a anti-CD20 antibody over Demiden in view of Hagenbeek.

With regard to the secondary reference, Reff, the applicant respectfully submits that this reference also does little to overcome the failings of the primary document (Demiden) and the secondary reference (Hagenbeek). Specifically, Reff teaches using plasmid constructs **to create chimeric anti-CD20 antibodies. In contrast, the applicant teaches using fusion protein immunoconjugate comprising an anti-CD20 antibody or fragment thereof and a non-related IFN-α-2a protein component**. Thus, Reff does nothing to overcome the failings of Demiden's teachings that anti-CD20 antibody be used in combinational therapies to modify B-cell lymphoma cells for purposes making these cells susceptible to cytotoxic agents. Reff provides no teaching or suggestion to overcome Hagenbeek's teaching that interferon is also allegedly useful in combination therapies with chemotherapeutic agents. None of these references teach the applicant's one step method of using the disclosed fusion protein (*i.e.*, anti-CD20 antibody or fragment thereof fused with IFN-α-2a) **to directly target B cell lymphoma cells using the subject's own cell-mediated cytotoxic cells** (*i.e.*, NK cells, macrophages *etc.*).

In conclusion, the applicant submits that Demiden either alone or in combination with Hagenbeek and Reff neither teach or suggest the applicant's claimed invention Accordingly, without such teaching or suggestion, the examiner has not established a prima facie case of obviousness. In view of the foregoing amendment and remarks, the applicant respectfully submits that the rejection of claims 16 and 17 under 35 U.S.C. §103(a) over Demiden in view of Hagenbeek and Reff has been overcome, and a similar rejection of new claims 23-27 on the same grounds would be improper.

*Davis in view of Taji*

With regard to Davis in view of Taji, the examiner alleged that Davis teaches a combination therapy using anti-CD20 antibody IFN, which has synergistic effects in humans. The examiner asserted that Taji teaches that anti-CD20 antibody enhances apoptosis of B lymphoma cells. The examiner further alleged that it would have been obvious to one of ordinary skill to made and use an anti-CD20 antibody or fragment thereof that is fused at its carboxy terminus to IFN-α-2a in a method to enhance apoptosis of B cell lymphoma cells. The examiner concluded that one of skill would have a reasonable expectation of success in treating lymphoma using this construct since it was well known how to construct an anti-CD20 antibody expression construct. In addition, the examiner asserted that one of skill would be motivated to minimize painful injections by giving one fusion protein instead of two separate protein injections.

The applicant submits that the primary reference Davis fails to teach or suggest a method of enhancing apoptosis of a target cell by administering a therapeutically effective amount of an immunoconjugate to a subject, wherein said immunoconjugate comprises an anti-CD20 antibody or an immunogenic fragment thereof that binds to CD20 expressed by a target cell that is to be eradicated, wherein said anti-CD20 antibody or immunogenic fragment thereof possesses human effector function, and further wherein said anti-CD20 antibody or immunogenic fragment thereof is fused as its carboxy terminus to IFN-α-2a that binds a receptor expressed on the surface of an effector cell. Unlike Davis, the applicant's method uses a protein comprising an anti-CD20 antibody or fragment thereof fused at its carboxy terminus to IFN-α-2a to treat B-cell lymphoma. The applicant's method unexpectedly provides an improved immunoconjugate that not only enhances antibody-dependent cellular cytotoxicity and phagocytic activities, but also lowers the toxicity and increases the serum half-life. The fusion protein, as opposed to the separate administration of IFN and anti-CD20 antibody as taught in Davis, simultaneously **targets B-cell lymphoma cells as well as uses the subject's effector cells** (*i.e.*, NK cells, macrophages *etc.*) **to kill** the targeted B-cell lymphoma cells. The anti-CD20 antibody of Davis is not fused to IFN-α-2a, and therefore would not specifically target IFN-α-2a to a tumor cell. Thus, Davis' method lacks specific targeting and simultaneous recruiting of effector cells to kill B cell lymphoma cells as claimed by the applicant.

Specifically, the applicants' method of enhancing apoptosis of target cells efficiently uses a 1:1 ratio of anti-CD20 antibody or fragments thereof with IFN-α-2a. This novel fusion

protein minimizes free IFN and simultaneously targets, and recruits effector cells, which destroy B-cell lymphoma cells. As discussed above, the applicant submits that fusing IFN-α-2a to the carboxy terminal of a CD-20 antibody has never been suggested or taught in the art at the time of filing. Davis neither teaches nor suggest such cloning methods and the relevance of cloning anti-CD20 antibody fusions was not known at the time of filing. Accordingly, the applicants submit that one of skill studying the disclosure of Davis would not be taught or even suggested to practice the claims invention.

With regard to the secondary reference, Taji, the applicants respectfully submit that this reference does little to overcome the failings of the primary document (Davis). Specifically, Taji does not teach the method of enhancing apoptosis of B-cell lymphoma cells by using an immunoconjugate that comprises anti-CD20 antibody fused with IFN-α-2a to simultaneously target B-cell lymphoma cells and recruit effector cells such as natural killer cells or macrophages to the bound target B-cell lymphoma cell. Rather, Tilg teaches using a **chimeric anti-CD20 antibody** (consisting of human immunoglobulin G 1-κ constant regions and variable regions from murine anti-CD20 antibody) to study this chimeric antibodies role in inducing apoptosis to inhibit B-cell lymphoma cell lines. The applicant submits that neither Davis nor Tilg teach or suggest the claimed method of using the applicants' immunoconjugate to pinpoint and kill B-cell lymphoma cells at the same time. Thus, one of skill **would not** reasonably expect improved success of the IFN/anti-CD20 antibody fusion protein based upon the contradictions of Davis in view of Taji, nor be motivated to reduce the number of painful administrations of the two different proteins (*i.e.*, interferon and anti-CD20 antibody) to treat B-cell lymphoma.

In summary, the applicants submit that Davis in view of Tilg neither teaches nor suggests the applicants' claimed invention. Accordingly, without such teaching or suggestion, the examiner has not established a prima facie case of obviousness. In view of the foregoing amendment and remarks, the applicants respectfully submit that the rejection of claims 16 and 17 under 35 U.S.Cl §103(a) over Davis in view of Tilg has been overcome, and a similar rejection of claims 23-27 on the same grounds would be improper.

## IV. CONCLUSION

In view of the foregoing, the claims are now believed to be in form of allowance, and such action is hereby solicited. If any point remains which the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number below.

Respectfully submitted,

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